Claim 1 now refers to the antagonist which "binds an EphB receptor" with support for this recitation found on at least page 7, lines 3-10. Hence the cancellation of claim 3 as moot. Claim 23 is added and finds support on at least page 7, lines 20-22. In that the amendments do not introduce new matter, their entry is respectfully requested. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Oath/Declaration

The declaration is said to be defective because it has not been signed by the inventor. The declaration is presently being sent to the inventor for execution and will be submitted shortly. It is noted that a Notice to File Missing Parts requesting the executed declaration does not appear to have been issued by the PTO.

Section 102 - Caras *et al.*

Claims 1-4 and 6 are rejected under 35 USC Section 102(b) as being anticipated by Caras *et al.* WO96/13518 (hereinafter "Caras *et al.*").

This rejection is obviated by the amendment of claim 1 herein to refer to the antagonist which "binds an EphB receptor." Caras *et al.* describes AL-1 antagonists. AL-1 is a GPI-linked ligand that binds the EphA group receptor Rek7. Reconsideration and withdrawal of the Section 102 rejection based on Caras *et al.* is respectfully requested.

Section 102 - Pandey *et al.*

Claims 1 and 4 are rejected under 35 USC Section 102(b) as being anticipated by Pandey *et al. Science* 268:567-569 (1995).

This rejection is obviated by the amendment of claim 1 to refer to an antagonist that binds an EphB receptor. Reconsideration and withdrawal of the Section 102 rejection based on Pandey *et al.* is respectfully requested.

Section 103(a)

Claims 1-6 are rejected under 35 USC Section 103(a) as being unpatentable

over Caras *et al.* in view of Wang *et al. Cell* 93: 741-753 (1998) (hereinafter "Wang *et al.*").

The Examiner contends that it would have been *prima facie* obvious to modulate the methods of Caras *et al.* so as to include the antibody that binds the EphB4 receptor in view of the teachings of Wang *et al.* The Examiner opines that one would have been motivated to do so because it was allegedly well known in the art that Eph receptors comprise two families - A class receptors and B class receptors - and that Eph-A-class receptors and their ligands are implicated in angiogenesis. The Examiner opines that it would have been obvious to modulate the method of Caras *et al.* so as to prevent angiogenesis by further including an antibody against the B-class receptors so as to prevent its ligand (ephrin-B2) from interacting with the EphB4 receptor.

Applicants respectfully submit that the presently claimed method is patentable over the cited references.

Claim 1 as amended herein refers to inhibiting angiogenesis in a mammal with an Eph receptor antagonist where that antagonist binds an EphB receptor. Preferably, the ErbB receptor is the ErbB4 receptor (claim 23 added herein). There was nothing in the art cited which would have suggested that an antagonist which binds an EphB receptor could inhibit angiogenesis in a mammal.

On page 23 cited by the Examiner, Caras *et al.* describes AL-1 antagonists (anti-AL-1 neutralizing antibodies, REK7-IgG fusion protein, and soluble AL-1 receptor) which all bind to AL-1 ligand, as opposed to an EphB receptor. AL-1 is a GPI-linked ligand which binds the Rek7 receptor (also known as the EphA5 receptor). The Rek7 receptor is an EphA group receptor as opposed to an EphB group receptor. See Example 9 on page 43 of Caras *et al.* as well as page 6, lines 26-31, and page 7, lines 3-10 of the present application.

Wang *et al.* found that targeted disruption of the *ephrin-B2* gene that

encodes the ephrin-B2 ligand in knockout mice prevented the remodeling of veins and arteries. Wang *et al.* reported that ephrin-B2 marked arterial but not venous endothelial cells, whereas Eph-B4 receptor marked veins but not arteries. See abstract of Wang *et al.* Moreover, Wang *et al.* stated that targeted disruption of *Eph-B4* was needed to determine the role of this receptor (sentence bridging columns 1-2 on page 750 of Wang *et al.*).

Applicants submit that the combination of Caras *et al.* and Wang *et al.* would not have suggested the use of an anti-Eph receptor antagonist to inhibit angiogenesis in a mammal. In particular, since the references failed to demonstrate the role of an EphB receptor, such as EphB4 receptor, in angiogenesis and did not describe an antagonist which bound an EphB receptor or use of such an antagonist to inhibit angiogenesis, Applicants submit that the presently claimed method would have been nonobvious over the cited references. Aside from these deficiencies of the combined art, Applicants submit that the claimed methods are patentable in that one could not have predicted with a reasonable expectation of success prior to the present application that it was possible to inhibit angiogenesis in a mammal by administering thereto an effective amount of an EphB-binding antagonist.

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Reconsideration and withdrawal of the Section 103 rejection is respectfully requested.

Respectfully submitted,
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Serial No.: 09/442,898

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (Amended) A method of inhibiting angiogenesis in a mammal comprising administering to the mammal an amount of an Eph receptor antagonist which is effective for inhibiting angiogenesis in the mammal, **wherein the antagonist binds an EphB receptor**.

Claim 3 has been cancelled.

Claim 23 has been added:

--23. The method of claim 1 wherein the antagonist binds EphB4 receptor.--